REMARKS

Claims 1-15 were filed with the application on April 11, 2001, and are currently pending.

Rejections Under 35 U.S.C. § 112

Second Paragraph

Claims 1-15 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Specific issues are addressed below in the order in which they were raised in the Office Action.

Regarding the term "complementarity": Applicants submit that the term is well known in the field of molecular docking, as shown by the mention of steric complementarity in the Rarey article cited in the Office action, which appears on page 486, last two paragraphs and page 487, first paragraph of the reference. ("This approach is based on the hypothesis that steric complementarity is a good descriptor for protein-ligand complexes.") Steric complementarity refers to how well the shape of the ligand fits in the binding site, but the general term is not limited to a single subtype of complementarity, and includes other subtypes, such as electrostatic complementarity and/or hydrogen bonding complementarity. Accordingly, applicants submit that the claim is not indefinite.

Regarding "plurality of ligands" in claims 1, 6 and 11: The claims are amended to recite "said plurality of ligands" in order to clarify that steps for analyzing the ligands are directed to ligands of the specified combinatorial library.

Regarding the term "hot spots" in claims 5, 10 and 15, the term is defined in the specification in paragraph 0034 as points in the binding site that are favorable for a polar or apolar atom of the ligand to bind. Regarding the term "pre-docking" in claims 5, 10 and 15, this term is now deleted.

Finally, regarding claims 6-10 and 12-15, errors in the claim dependencies are now corrected, so that claims 7-10 depend from claim 6, and claims 12-15 depend from claim 11.

Applicants submit that the above amendments and remarks clarify the meaning of the claims so that the invention is not indefinite. It is believed that the rejection is hereby overcome.

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First Paragraph: Lack of Enablement

Claims 1-15 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. The rejection is traversed.

The Office Action states on page 5, paragraph 12 that "it would be unpredictable for one skilled in the art to use the method, system, or program storage device of this instant application to assess combinatorial libraries based on the observed crystallographic data of any other receptor beyond the ones of the instant application. In light of the difficulty of the protein crystallization process, it is, therefore, unreasonable to expect one skilled in the art to use the method, system, or a program storage device that relies on observed crystallographic data produced from an unpredictable process to predictably assess combinatorial libraries using crystallographic data directed to any other target receptor without undue experimentation". With respect, applicants disagree, and submit that the claimed invention is fully enabled, as the specification and claims completely describe method, systems and program storage devices for assessing the potential activity/potency of compounds of a combinatorial library with respect to a particular target molecule. The method is exemplified in the specification for docking of compounds of a 4-aspartyl protease inhibitor library into the binding sites of plasmepsin and cathepsin, and also for docking of 103 known ligands of protein-ligand complexes having a known structure into the binding sites of the protein (pages 14-38). The 103 structures were retrieved from the Protein Data Bank (PDB), a public repository of structural information for protein-ligand complexes, obtained from x-ray crystallography or NMR studies. The PDB contained 22516 structures of biological molecules, in the categories of Proteins, Peptides, and Viruses (20321), Protein/Nucleic Acid Complexes (945), Nucleic Acids (1232) and Carbohydrates (18) as of September 16, 2003, and new structures are being added at the rate of about 3,000 per year. While applicants admit that the docking procedures of the invention do require a target molecule with a known active binding site and for which the three-dimensional structure is known or can be extrapolated by homology from known structures of chemically similar materials, it is submitted that the claimed method is fully enabled with respect to these known targets, and that no experimentation is required to practice the invention. Furthermore, these targets are relatively plentiful at the present, and can be expected to become even more so in the future. It is believed that the rejection is hereby overcome.

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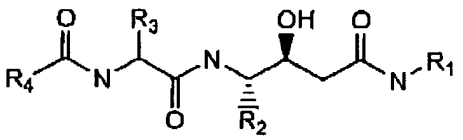
Rejections Under 35 U.S.C. § 103

Claims 1-15 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Ho *et al.* (1994) in view of Rarey *et al.* (*J. Mol. Biol.*, 261, 470-489 (1996)), either alone or in combination with DeLisi et al. (U.S. Patent No. 5,495,423) or Aldenderfer *et al.* (1984). The rejection is traversed.

Both Ho and Rarey disclose molecular docking procedures for individual ligands only. Ho describes stepwise assembly of a structure in the binding site to result in individual compounds that contain specified pharmacophoric elements. Rarey describes validation of the FlexX docking method using a set of known protein-ligand complexes taken from the PDB. Individual ligands were docked to the protein to obtain predicted structures, and these were compared to the observed structure in order to determine whether the docking procedure effectively predicted actual individual structures. Both of the references are silent regarding docking compounds of a combinatorial library, and assessing whether the library *as a whole* is likely to contain a significant number of compounds that bind to a particular target.

Furthermore, while Rarey compares the position of the predicted structures of individual compounds in the binding site to the actual structure using rms deviation between the positions of each, the claimed invention compares the position of the *common core* of each compound as docked in the binding site with the position of the *common core* of other compounds in the library in the binding site. In the context of the present invention, 'common core' refers to a structure or scaffold to which are attached varied substituents, thereby forming the compounds of the library. (See paragraph 0027 of the specification.) For example, the common core of the actual libraries described in the present application is the pepstatin scaffold shown below. The R groups represent the variable substituents.



The specification describes on pages 27-38 the results of docking compounds of four actual libraries and eight virtual libraries based on the pepstatin common core shown above. Clusters were formed using the calculated rms deviation between positions of the scaffold in the binding site for pairs of docked compounds, and the libraries were ranked according to the percentage of compounds in the largest cluster.

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In summary, the primary and secondary references are completely silent regarding combinatorial libraries, determining whether compounds of the library are likely to bind to a particular target, and the particular technique used by the claimed invention to make such an assessment. These deficiencies are not supplied by the other cited references. Therefore, applicants submit that the claims are not obvious over any combination of the references. It is believed that the rejection is hereby overcome.

In view of the above amendments and remarks, applicants respectfully request allowance of all claims pending herein.

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Respectfully submitted,

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